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Chemotherapy in Viral and Rickettsial Disease

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SUMMARY

Aureomycin and chloromycetin have now been used in a number of viral and rickettsial diseases and have gone far toward fulfilling their original promise. In local trials aureomycin has been shown to be a very effective drug in primary atypical pneumonia, and a valuable drug in Q fever. A small number of cases of psittacosis appear to have responded favorably to aureomycin. The search for chemotherapeutic compounds which may be effective in other viral diseases has been sharply stimulated by these developments.

AT the time of the meeting of the California Medical Association in April of 1948 there were rumors that the whole outlook in the treatment of rickettsial and, perhaps, some viral diseases was about to be transformed. These arose from reports on experimental trials with two new antibiotic drugs, chloromycetin and aureomycin. During the ensuing year these drugs were tried by numerous groups of workers in a variety of diseases, and it is now safe to state that both have gone a long way toward fulfilling their promise.

Prior to 1948 the only drugs of proved effectiveness against viral diseases of man were the sulfonamides and penicillin.* These had a relatively limited field of usefulness in certain diseases caused by the largest viruses. Sulfonamide drugs had been found useful in trachoma and inclusion conjunctivitis, against two strains of psittacosis virus, and in lymphogranuloma venereum. Penicillin, in large doses, had been shown to be effective in psittacosis.

In the rickettsial field paraminobenzoic acid had been shown to modify the course of several diseases, but its effectiveness was relatively low. Streptomycin had shown some promise in experimental animals, but had not produced any startling results in human infections. Extensive search had failed to disclose other compounds which were both effective and safe for use. The viruses of medium and small size remained unaffected by chemotherapeutic agents.

It is not within the scope of this paper to cover all the reported trials of aureomycin and chloromycetin in viral and rickettsial diseases. It is sufficient to state that there is now evidence that the former is effective in Q fever, typhus, Rocky Mountain spotted fever, rickettsialpox, lymphogranuloma venereum, psittacosis, and primary atypical pneumonia, and that the latter is effective in the rickettsial diseases listed above and in scrub typhus as well. Emphasis in this presentation will be placed on data taken from local investigations which illustrate the effectiveness of aureomycin and on a discussion of the significance of recent developments. The data on aureomycin in primary atypical pneumonia, Q fever, and psittacosis are taken from the combined

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*For references in this field prior to 1948 the reader is referred to "Viral and Rickettsial Diseases of Man," edited by T. M. Rivers, J. B. Lippincott Co., Phila., 1948. The more recent literature has been reviewed by Brainerd, H. D., Lennette, E. H., Meiklejohn, G., Bruyn, H. B., and Clark, W. C. The Clinical Evaluation of Aureomycin, Proceedings of the Second National Symposium on Recent Advances in Antibiotic Research. J. Clin. Invest., 28:992-1005, Part I (Sept.), 1949.

studies of the Viral and Rickettsial Disease Laboratory of the State Department of Public Health and the Infectious Disease Laboratory, San Francisco Hospital.

PRIMARY ATYPICAL PNEUMONIA

A sharp increase in the incidence of this most common form of viral pneumonia has provided an excellent opportunity to evaluate aureomycin. More than 50 patients with this diagnosis have been treated since last fall. Of these 50, 22 were included in a carefully controlled study. The remainder were treated in various areas without controls. It might be noted that the literature on aureomycin is somewhat remarkable in that none of the work reported to date has been controlled in a satisfactory manner.

Considering first the uncontrolled series, the response in these patients has been so uniformly favorable that, when the data obtained are combined with those from similar reported series, one would have to be extremely cynical to hold that the drug was not effective. Rapid symptomatic improvement followed by defervescence within from one to three days has been the rule. One is justified in withholding judgment on the effectiveness of the drug only because the course of primary atypical pneumonia is subject to such pronounced variation and because recovery without treatment occurs so frequently soon after medical aid is sought. It is for this reason that the results of a controlled study are of particular interest.

The occurrence of cases of primary atypical pneumonia in large numbers at Fort Ord during the winter of 1948-49 made such a study possible. Under the auspices of the Commission on Influenza of the Army Epidemiological Board patients admitted to the Station Hospital with primary atypical pneumonia of a relatively severe degree were treated alternately with aureomycin or penicillin. Penicillin was used in the control group because it was considered advisable to cancel out any therapeutic success which aureomycin might have if patients with bacterial pneumonias were inadvertently included in the study group. There is convincing evidence that penicillin does not alter the course of the great majority of cases of primary atypical pneumonia. The criteria used in the selection of patients are included in a detailed report on this study.[1]

In the 20 patients composing the penicillin-treated group the duration of the illness followed the pattern previously observed in untreated patients. Approximately one-third became afebrile within 72 hours. The remainder continued to be febrile for longer periods of time, exceeding five days in seven instances, with a maximum in one individual of 23 days after initiation of treatment. Twelve of the 20 patients in this group were shown to have cold hemagglutinin titers of 1:32 or more.

In contrast, of 18 patients treated initially with aureomycin, 13 were afebrile within 48 hours, four more within 96 hours, and a single patient within 120 hours. Symptomatic improvement was observed considerably earlier than defervescence. Clinical relapses were observed in three patients after aureomycin was discontinued. In each instance prompt recovery followed reinstitution of aureomycin therapy. In an additional group of four patients, who had been treated initially with penicillin and had become alarmingly ill while receiving this drug, prompt recovery followed within 48 hours after aureomycin was substituted for penicillin.

The results of this study leave little doubt that aureomycin is an exceedingly effective chemotherapeutic agent in the more severe cases of primary atypical pneumonia. Responses obtained compare favorably with those observed in cases of pneumococcal pneumonia treated with penicillin. The ineffectiveness of the latter drug in primary atypical pneumonia is well brought out by the results outlined. It is reasonable to suppose that aureomycin will be effective in milder cases of primary atypical pneumonia and may prove useful in those upper respiratory infections which are caused by the same virus.

Q FEVER

A preliminary report on the use of aureomycin in Q fever has already been published. The results obtained in a group of 15 acutely ill patients were generally favorable, and in only one instance was there a frank therapeutic failure. Relapse was noted in two patients in this group after treatment was stopped.

Treatment of a larger group of patients since that report was prepared has made it clear that the therapeutic margin of aureomycin in Q fever may be narrow and that, even with combined therapy using large oral and intravenous doses of the drug, a certain proportion of therapeutic failures may occur. Relapse also occurs in a certain proportion of cases. It is, of course, possible that strains of Coxiella burneti may vary widely in sensitivity to aureomycin in the same way as do many bacteria. Experience to this time indicates that aureomycin in Q fever is a useful, although by no means infallible, drug. Preliminary trials with chloromycetin are encouraging, but have not yet progressed to the point where evaluation is possible.

PSITTACOSIS

Three patients with diagnosis of psittacosis have been treated with aureomycin. In each instance prompt improvement has been observed following institution of aureomycin therapy. This is a very small number of cases, but the severity of untreated psittacosis in persons in the upper age groups is so uniformly high that the results carry considerable weight. It might be noted that in experimental studies aureomycin appears to have a margin over penicillin, which is also effective in human psittacosis when used in adequate dosage.

DISCUSSION

Results of the kind outlined herein, taken with those reported from other sources, point up the fact that previously held notions about the inaccessibility of intracellularly-situated infective agents to

chemotherapeutic drugs are no longer tenable. It is true that the rickettsiae and the psittacosis-lymphogranuloma group of viruses represent relatively large agents which may be closer in metabolic requirements to certain of the bacteria than to the smaller viruses. However, it cannot be disputed that they are organisms which, to date, have been shown to grow only within the living cell. The argument that viruses could not be reached for this reason is thus not valid.

Despite the fact that effective and safe drugs have not yet been found for the numerous viruses of medium size, such as influenza, or small size, such as poliomyelitis, the outlook has become considerably more promising. With those agents which attack tissues other than those of the central nervous system the prospects are, of course, better, because the potentialities of tissue regeneration are high and all that appears to be needed is a drug which can hold the infective agent in check until immunity develops. The neurotropic viruses pose a special problem, because it has been shown that dissemination of these viruses is widespread throughout irreplaceable nervous system tissues by the time clinical illness is apparent. Thus dramatic results from chemotherapy appear less likely. Chemoprophylaxis, on the other hand, may prove to be an effective procedure.

It might be noted that the investigations which have led to these advances have followed two general lines. One is scientific, and has pursued the study of viral and cell metabolism in an effort to obtain clues pointing to the accessible points of attack. The other has been a systematic screening of innumerable chemical compounds and antibiotic substances with a view to finding drugs which will be both effective and safe. To date the latter method has been the more rewarding and, in point of fact, all antibiotics in use at this time have developed from this type of approach. As knowledge increases, it is to be hoped that the former approach may in time prove to be equally or even more productive.

REFERENCE

1. Meiklejohn, G., and Shragg, R. I.: Aureomycin in primary atypical pneumonia; a controlled evaluation, J.A.M.A., 140:391-396 (May 28), 1949.